Application No. 10/088,814
Amendment Dated 12 August 2005
Reply to Office Action of 14 March 2005

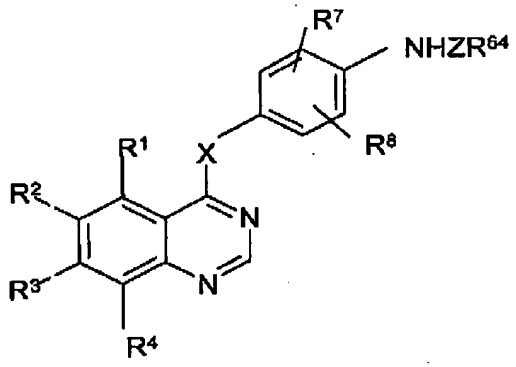
Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1-19. (Cancelled)

20. (Currently amended) A compound of formula (IIC)



or a salt, ester or amide thereof;

where X is NH~~O, or S, S(O) or S(O)$_2$, or NR^8 where R^8 is hydrogen or C$_{1-6}$alkyl~~;

Z is C(O) or S(O)$_2$;

R^{64} is ~~optionally substituted hydrocarbyl or optionally substituted heterocyclyl~~ optionally substituted aryl selected from phenyl optionally substituted with up to 5 groups selected from nitro, halo, carboxy, cyano, C$_{1-4}$alkyl, C$_{1-4}$alkoxy, C$_{1-4}$alkylthio, acetoxy, acetamido, hydroxy, aminosulphonyl, C$_{1-4}$alkylsulphonyl, trifluoromethyl, arC$_{1-10}$alkyl, or arC$_{1-10}$alkyloxy wherein aryl rings in the substituents may themselves be substituted with halo, nitro or C$_{1-4}$alkyl; optionally substituted C$_{3-6}$cycloalkyl selected from optionally substituted cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl any of which may be optionally substituted with nitro, halo, carboxy, cyano, C$_{1-4}$alkyl, C$_{1-4}$alkoxy, C$_{1-4}$alkylthio, acetoxy, acetamido, hydroxy, aminosulphonyl, C$_{1-4}$alkylsulphonyl, trifluoromethyl, arC$_{1-10}$alkyl, arC$_{1-10}$alkyloxy, or aryl wherein aryl rings in the substituents may themselves be substituted with halo, nitro or C$_{1-4}$alkyl; optionally substituted arC$_{1-10}$alkyl selected from optionally substituted benzyl, phenylethyl or phenylpropyl, wherein the phenyl ring is optionally substituted with up to 5 groups selected from nitro, halo, carboxy, cyano, C$_{1-4}$alkyl, C$_{1-4}$alkoxy, C$_{1-4}$alkylthio, acetoxy, acetamido, hydroxy, aminosulphonyl, C$_{1-4}$alkylsulphonyl, trifluoromethyl, arC$_{1-10}$alkyl, or arC$_{1-10}$alkyloxy wherein aryl

rings in the substituents may themselves be substituted with halo, carboxy, trifluoromethyl, nitro or C_{1-4}alkyl;
optionally substituted heterocyclyl selected from pyridyl, pyrazine, pyrimidinyl, pyrrolidino, furyl, tetrahydrofuryl, oxazolyl, morpholino, thiadiazole, indolyl, quinolinyl, isoquinolinyl, pyrazolyl, methylenedioxybenzyl, thiophene and benzothiophene, all of which may be optionally substituted with one or more groups selected from nitro, halo, carboxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, acetoxy, acetamido, hydroxy, aminosulphonyl, C_{1-4}alkylsulphonyl, trifluoromethyl, arC_{1-10}alkyl, or arC_{1-10}alkyloxy wherein aryl rings in the substituents may themselves be substituted with halo, carboxy, trifluoromethyl, nitro or C_{1-4}alkyl;
optionally substituted C_{1-10}alkyl where optional substituents for C_{1-10}alkyl include amino, mono- or di-C_{1-4}alkylamino, hydroxy, C_{1-4}alkoxy, heterocyclyl selected from thiophene, tetrahydrothiophene-1,1-dioxide, pyrrolidino, morpholino, furyl and tetrahydrofuryl, C_{1-4}alkoxy, acetamido, aryloxy, alkylC_{1-4}thio, aroyl where the aryl ring may itself be substituted with halo, carboxy, trifluoromethyl, nitro, carboxy or trifluoromethyl, C_{3-10}cycloalkyl or C_{3-10}cycloalkenyl; or optionally substituted C_{2-10}alkenyl or C_{2-10}alkynyl where optional substituents for C_{2-10}alkenyl or C_{2-10}alkynyl include nitro, halo, carboxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, acetoxy, acetamido, hydroxy, aminosulphonyl, C_{1-4}alkylsulphonyl, trifluoromethyl, arC_{1-10}alkyl, or arC_{1-10}alkyloxy wherein aryl rings in the substituents may themselves be substituted with halo, carboxy, trifluoromethyl, nitro or C_{1-4}alkyl; or such groups are substituted by aryl, where the aryl ring may itself be substituted with halo, nitro, carboxy, trifluoromethyl;
R^7 and R^8 are independently selected from hydrogen, halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxymethyl, di(C_{1-4}alkoxy)methyl, C_{1-4}alkanoyl, trifluoromethyl, cyano, amino, C_{2-5}alkenyl, C_{2-5}alkynyl, a phenyl group, a benzyl group or a 5-6-membered heterocyclic group with 1-3 heteroatoms, selected independently from O, S and N, which heterocyclic group may be aromatic or non-aromatic and may be saturated, and [[()]]linked via a ring carbon or nitrogen atom[()]], or unsaturated, and [[()]]linked via a ring carbon atom[()]], and which phenyl, benzyl or heterocyclic group may bear on one or more ring carbon atoms up to 5 substituents selected from hydroxy, halogeno, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkanoyloxy, trifluoromethyl, cyano, amino, nitro, C_{2-4}alkanoyl, C_{1-4}alkanoylamino, C_{1-4}alkoxycarbonyl, C_{1-4}alkylsulphanyl, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, carbamoyl, N-C_{1-4}alkylcarbamoyl, N,N-di(C_{1-4}alkyl)carbamoyl, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl, N,N-di(C_{1-4}alkyl)aminosulphonyl, C_{1-4}alkylsulphonylamino, and a saturated heterocyclic group selected from morpholino, thiomorpholino, pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl and pyrazolidinyl, which saturated heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno,

C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkanoyloxy, trifluoromethyl, cyano, amino, nitro and C_{1-4}alkoxycarbonyl, and

where R^1, R^2, R^3 and R^4 are independently selected from halo, cyano, nitro, trifluoromethyl, C_{1-3}alkyl, $-NR^{13}R^{14}$, [[(]]wherein R^{13} and R^{14}, which may be the same or different, each represents hydrogen or C_{1-3}alkyl[[)]], or $-X^1R^{15}$, [[(]]wherein X^1 represents a direct bond, -O-, $-CH_2-$, -OCO-, carbonyl, -S-, -SO-, $-SO_2-$, $-NR^{16}CO-$, $-CONR^{16}-$, $-SO_2NR^{16}-$, $-NR^{17}SO_2-$ or $-NR^{18}-$, [[(]]wherein R^{16}, R^{17} and R^{18} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl[[)]], and R^{15} is selected from one of the following groups:

1') hydrogen or C_{1-5}alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro or amino;

2') C_{1-5}alkylX^2COR^{19} [[(]]wherein X^2 represents -O- or $-NR^{20}-$, [[(]]in which R^{20} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl[[)]], and R^{19} represents C_{1-3}alkyl, $-NR^{21}R^{22}$ or $-OR^{23}$, [[(]]wherein R^{21}, R^{22} and R^{23} which may be the same or different each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl[[)]]];

3') C_{1-5}alkylX^3R^{24} [[(]]wherein X^3 represents -O-, -S-, -SO-, $-SO_2-$, -OCO-, $-NR^{25}CO-$, $-CONR^{25}-$, $-SO_2NR^{27}-$, $-NR^{28}SO_2-$ or $-NR^{29}-$, [[(]]wherein R^{25}, R^{26}, R^{27}, R^{28} and R^{29} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl[[)]], and R^{24} represents hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C_{1-3}alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl and C_{1-4}alkoxy[[)]];

4') C_{1-5}alkylX^4C_{1-5}alkylX^5R^{30} [[(]]wherein X^4 and X^5 which may be the same or different are each -O-, -S-, -SO-, $-SO_2-$, $-NR^{31}CO-$, $-CONR^{32}-$, $-SO_2NR^{33}-$, $-NR^{34}SO_2-$ or $-NR^{35}-$, [[(]]wherein R^{31}, R^{32}, R^{33}, R^{34} and R^{35} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl[[)]], and R^{30} represents hydrogen or C_{1-3}alkyl[[)]];

5') R^{36} [[(]]wherein R^{36} is a 5-6-membered saturated heterocyclic group, [[(]]linked via carbon or nitrogen[[)]], with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl and C_{1-4}alkylsulphonylC_{1-4}alkyl[[)]];

6') C_{1-5}alkylR^{36} [[(]]wherein R^{36} is as defined in (5') above[[)]];

7') C_{2-5}alkenylR^{36} [[(]]wherein R^{36} is as defined in (5') above[[)]];

8') C_{2-5}alkynylR^{36} [[(]]wherein R^{36} is as defined in (5') above[[)]];

9') R^{37} [[(]]wherein R^{37} represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group, [[(]]linked via carbon or nitrogen[[)]], with 1-3 heteroatoms selected from O, N

and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents on an available carbon atom selected from hydroxy, halogeno, amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, trifluoromethyl, cyano, $-CONR^{38}R^{39}$ and $-NR^{40}C(O)OR^{41}$, [[(I]]wherein R^{38}, R^{39}, R^{40} and R^{41}, which may be the same or different, each represents hydrogen, C_{1-4}alkyl or C_{1-3}alkoxyC_{2-3}alkyl[[)]];

10') C_{1-5}alkylR^{37} [[(I]]wherein R^{37} is as defined in (9') above[[)]];

11') C_{2-5}alkenylR^{37} [[(I]]wherein R^{37} is as defined in (9') above[[)]];

12') C_{2-5}alkynylR^{37} [[(I]]wherein R^{37} is as defined in (9') above[[)]];

13') C_{1-5}alkylX^6R^{37} [[(I]]wherein X^6 represents -O-, -S-, -SO-, $-SO_2$-, $-NR^{42}CO$-, $-CONR^{43}$-, $-SO_2NR^{44}$-, $-NR^{45}SO_2$- or $-NR^{46}$-, [[(I]]wherein R^{42}, R^{43}, R^{44}, R^{45} and R^{46} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl[[)]], and R^{37} is as defined hereinbefore[[)]];

14') C_{2-5}alkenylX^7R^{37} [[(I]]wherein X^7 represents -O-, -S-, -SO-, $-SO_2$-, $-NR^{47}CO$-, $-CONR^{48}$-, $-SO_2NR^{49}$-, $-NR^{50}SO_2$- or $-NR^{51}$-, [[(I]]wherein R^{47}, R^{48}, R^{49}, R^{50} and R^{51} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl[[)]], and R^{37} is as defined in (9') above[[)]];

15') C_{2-5}alkynylX^8R^{37} [[(I]]wherein X^8 represents -O-, -S-, -SO-, $-SO_2$-, $-NR^{52}CO$-, $-CONR^{53}$-, $-SO_2NR^{54}$-, $-NR^{55}SO_2$- or $-NR^{56}$-, [[(I]]wherein R^{52}, R^{53}, R^{54}, R^{55} and R^{56} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl[[)]], and R^{37} is as defined hereinbefore[[)]];

16') C_{1-3}alkylX^9C_{1-3}alkylR^{37} [[(I]]wherein X^9 represents -O-, -S-, -SO-, $-SO_2$-, $-NR^{57}CO$-, $-CONR^{58}$-, $-SO_2NR^{59}$-, $-NR^{60}SO_2$- or $-NR^{61}$-, [[(I]]wherein R^{57}, R^{58}, R^{59}, R^{60} and R^{61} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl[[)]], and R^{37} is as defined hereinbefore[[)]]; and

17') C_{1-3}alkylX^9C_{1-3}alkylR^{36} [[(I]]wherein X^9 and R^{36} are as defined in (5') above[[)]];

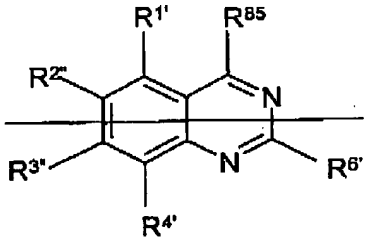
provided that i) where R^1, R^4, R^7 and R^8 are all hydrogen and R^2 and R^3 are both hydrogen or both methoxy, R^{64} is other than phenyl; ~~and~~

(ii) where R^1, R^4, ~~R^6~~, R^7 and R^8 are all hydrogen and R^2 and R^3 are methoxy, and Z is C(O), R^{64} is other than methyl; and

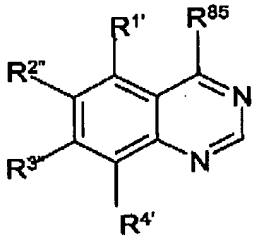
iii) wherein at least one of R^1-R^4 is $-X^1R^{15}$.

21-26. (Cancelled)

27. (Currently amended) A method for preparing a compound according to claim 20~~19~~, which method comprises reacting a compound of formula (VIII[[']])

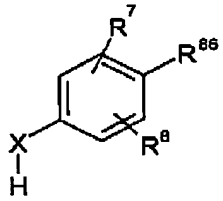


~~(VIII')~~



(VIII)

where $R^{1'}$ is equivalent to the corresponding group of formula R^1 as defined in relation to the said compound of claim 20~~19~~, or a precursor thereof;
$R^{2'}$ is equivalent to the corresponding group of formula R^2 ~~or $R^{2'}$ or R^{68}~~ as defined in relation to the said compound of claim 20~~19~~, or a precursor thereof;
$R^{3'}$ is equivalent to the corresponding group of formula R^3 ~~or $R^{3'}$ or R^{69}~~ as defined in relation to the said compound of claim 20~~19~~, or a precursor thereof;
$R^{4'}$ is equivalent to the corresponding group of formula R^4 as defined in relation to the said compound of claim 20~~19~~, or a precursor thereof;
~~$R^{6'}$ is a group R^6 where present in the compound of claim 19,~~ and R^{85} is a leaving group, with a compound of formula (IX')



(IX')

where X, R^7 and R^8 are as defined in relation to the ~~relevant~~ said compound according to claim 20, and R^{88} is a group of formula $NHZR^{64}$ where Z and R^{64} as are defined in ~~the~~ relation to the said compound in claim 20~~19~~; and thereafter if desired or necessary converting a group $R^{1'}$, $R^{2'}$,

$R^{3'}$ or $R^{4'}$ to a group R^1, R^2 ~~or $R^{2'}$ or R^{6B}~~, R^3 ~~or $R^{3'}$ or R^{6B}~~ and R^4 respectively or to a different such group.

28-29. (Cancelled)

30. (Currently amended) A pharmaceutical composition comprising a compound of formula (IICA) as defined in claim 20~~19~~, or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester, or amide thereof, in combination with at pharmaceutically acceptable carrier.

31-33. (Cancelled)

34. (Currently amended) A compound according to claim 20, wherein R^{64} is phenyl, 2-furan, (E)-CH=CH-phenyl, 3,4,5-trimethoxyphenyl, 2,4-difluorophenyl, 2-nitro-4,5-dimethoxyphenyl, 2,4-dinitrophenyl, 2-fluorobenzyl, cyclopentyl, 1-methylbut-3-enyl, ~~CH_2CN,~~ n-heptyl, 2-(methylthio)ethyl, 2-ethoxyethyl, $C(CH_3)=CH_2$, 5-methyl-2-pyrazine, 3-furyl, 3-cyanophenyl, 4-acetoxyphenyl, 2-nitro-3-methoxyphenyl, 2-methylthiophenyl, 3-acetoxyphenyl, ~~4-aminosulphenyl-1-hydroxy-2-naphthyl,~~ 2-pyridyl, 2-quinolinyl, 1,5-dimethyl-1H-pyrazolyl, 2-fluoro-5-nitrophenyl, 3-pyridyl 2-chloro-3-pyridyl, 2-fluorophenyl, 2,3-difluorophenyl, 2,5-difluorophenyl, 2,3-dimethoxyphenyl, 3,5-dimethoxy-4-hydroxy-phenyl, 3-chloro-4-carboxyphenyl, 3-nitro-4-(methylsulphonyl)-phenyl, 3-nitro-4-methoxyphenyl, (E)-CH=CH-(2-nitrophenyl), (E)-CH=CH-(3-nitrophenyl), (E)-CH=CH-(4-nitrophenyl), (E)-CH=CH-(4-chlorophenyl), (E)-CH=CH-(2,3,4-trifluoro-phenyl), (E)-CH=CH-(3-(trifluoromethyl)phenyl), (E)-CH=CH-(4-fluorophenyl), 2-indolyl, 5-fluoro-2-indolyl, 3-fluorophenyl, 3,5-dinitrophenyl, 3-(trifluoromethyl)benzyl, 3-fluorobenzyl, 4-chlorobenzyl, 4-methoxybenzyl, 4-(*iso*-propyl)benzyl, 3-nitrobenzyl, 2-phenoxyethyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-(4-chlorobenzoyl)ethyl, ~~3-chloro-1-propyl~~ 3-phenoxy-1-propyl, 3-phenyl-1-propyl, 3-benzoylpropyl, dec-9-enyl, 1-methylbut-1-enyl, (2-thiophene)methyl, (3-thiophene)methyl, 2-(3-nitro-4-hydroxyphenyl)ethyl, 3,5-difluorobenzyl, ~~4-phenylbenzyl,~~ 3,4-methylenedioxybenzyl, 2,6-difluorobenzyl, 4-(n-butoxy)benzyl, 3-methyl-1-butyl, pent-4-ynyl, ~~3-phenoxybenzyl,~~ 3-(5-bromo-4-methoxy)thiophene, 3-(5-chloro-4-methoxy)-thiophene, 3-methoxy-4-ethoxybenzyl, 4-(benzyloxy)benzyl, 3-(2-thiophene)propyl, hex-5-ynyl, 1-(4-chlorophenyl)cyclopropyl, cyclopentylmethyl, 2-(cyclopentyl)ethyl, cyclohexylmethyl, 2-(cyclohexyl)ethyl, 3-(cyclohexyl)propyl, 1-phenoxyethyl, (E)-C(CH_3)=CH-phenyl, 2-chloro-5-nitrophenyl, methyl, n-heptyl, 2-furyl, 3-furyl, (2-thiophene)methyl, 2-indolyl,

2,4-difluorophenyl, (3-nitro-4-(methylsulphonyl))-phenyl, pent-4-ynyl, 5-methyl-2-pyrazinyl, cyclopentyl, ~~(cyclohexyl)methyl~~, 3-nitro-4-methoxyphenyl, 2-tetrahydrofuryl, 2-pyridyl, 3-pyridyl, ~~(E)-CH=CH-(4-nitrophenyl),~~ 1,5-dimethyl-pyrazol-3-yl, cyclobutyl, 2-methoxyphenyl, 3-nitrophenyl, 4-nitrophenyl, cyclohexyl, ~~4-nitropyrrol-2-yl,~~ 3-nitro-4-methylphenyl, 3-nitro-4-fluorophenyl, (3-thiophene)methyl, 3-chloro-2-benzothiophene, 5-chloro-2-indolyl, ~~(1-piperidine)ethyl, 3,4-methylenedioxyphenyl,~~ but-3-ynyl, 3-cyanophenyl, 2-(acetamido)ethyl, 4-(trifluoromethyl)phenyl, 3-chloro-4-fluorophenyl, 4-fluoro-3-(trifluoromethyl)-phenyl, 4-fluorophenyl, 5-bromo-2-thiophene, 4-methoxyphenyl, 6-methyl-3-pyridyl, 5-nitro-2-furyl, 2-nitrophenyl, (E)-CH=CH-(3-chlorophenyl), 2-thiophene, cyclopropyl, 3-methylphenyl, 2-chlorophenyl, 2-fluorophenyl, 2,5-dichlorophenyl, 3-fluorophenyl, 6-chloro-3-pyridyl, 5-bromo-2-furyl, 3-nitro-2-methylphenyl, 3-chlorophenyl, 3-(tetrahydrothiophene-1-1'-dioxide)methyl, 2-methoxyethyl, or 2-(methylthio)phenyl.

35. (Previously presented) A compound according to claim 20, where R^{64} is phenyl or halosubstituted phenyl.

36. (Currently amended) A compound according to claim 2033, where R^1 is hydrogen and R^4 is halo, C_{1-4}alkyl or C_{1-4}alkoxy.

37. (Currently amended) A compound according to claim 2033, where X^1 is oxygen.

38. (Currently amended) A compound according to claim 2033, where R^{15} is selected from a group (1'), (3'), (6') or (10') as defined in claim 204.

39. (Currently amended) A compound according to claim 2033, where R^7 and R^8 are independently selected from hydrogen, halo, C_{1-4}alkoxy, cyano, trifluoromethyl or phenyl.

40. (Currently amended) An *in vivo* hydrolysable ester of a compound according to claim 2033, which is a phosphate ester.

41. (New) A compound according to claim 20 where R^1 is hydrogen, R^4 is halo, C_{1-4}alkyl or C_{1-4}alkoxy, X^1 is oxygen, R^{15} is selected from a group (1'), (3'), (6') or (10') as defined in claim 20 and R^7 and R^8 are independent y selected from hydrogen, halo, C_{1-4}alkoxy, cyano, trifluoromethyl or phenyl.

42. (New) A compound according to claim 41 where R^{64} is phenyl or halosubstituted phenyl.

43. (New) A compound according to claim 34 wherein R^1 is hydrogen, R^4 is halo, C_{1-4}alkyl or C_{1-4}alkoxy, X^1 is oxygen, R^{15} is selected from a group (1'), (3'), (6') or (10') as defined in claim 20 and R^7 and R^8 are independently selected from hydrogen, halo, C_{1-4}alkoxy, cyano, trifluoromethyl or phenyl.

44. (New) A method of treating colorectal or breast cancer in a warm blooded animal in need of such treatment, which comprises administering to said animal an effective amount of a compound of formula (IC), as claimed in claim 20.